Public health significance of four cardiovascular risk factors assessed 25 years ago in a low prevalence country

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Abstract: Background: The individual and combined effect of cardiovascular disease (CVD) risk factors (RFs) on CVD mortality varies between populations. Our aim was to examine this association and its public health impact in Switzerland, a country with comparably low CVD mortality. Methods: We included 9853 men and women aged 25-74 years who participated in the Swiss MONICA (MONItoring of trends and determinants in CArdiovscular disease) study (1983-1992) and were followed up for survival until 2008. Adjusted Cox regression was used to calculate CVD mortality hazard ratios (HR). CVD-RFs were obesity (body mass index 30 kg/m(2)), smoking (1 cig/d), high blood pressure (140 or 90 mmHg), and total: high-density lipoprotein cholesterol ratio (5.0). Besides age and sex, models were adjusted for diet, physical activity, educational class, marital status, and the respective other CVD-RFs. Results: After adjustment for age and sex, the HR of CVD death was for obesity 1.86 (95% CI 1.50-2.31), for smoking 1.63 (95% CI 1.32-2.01), for high blood pressure 1.42 (95% CI 1.16-1.73), and for high cholesterol ratio 1.30 (95% CI 1.06-1.60). Adjustment for other covariates moderately attenuated estimates. CVD-RFs had an independent and synergistic effect and accounted for 43.0% of population attributable risk. The presence of all four compared to zero CVD-RFs was associated with a 9.6 years shorter expected survival for a man aged 50. Conclusions: Most CVD deaths could be avoided by prevention of four traditional CVD-RFs. Reduction of smoking prevalence and avoidance of weight gain in the population are the most effective measures. Particular attention should be dedicated to persons with multiple CVD-RFs.

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Results
After adjustment for age and sex, the HR of CVD death was for obesity 1.86 (95% CI 1.50–2.31), for smoking 1.63 (95% CI 1.32–2.01), for high blood pressure 1.42 (95% CI 1.16–1.73), and for high cholesterol ratio 1.30 (95% CI 1.06–1.60). Adjustment for other covariates moderately attenuated estimates. CVD-RF had an independent and synergistic effect and accounted for 43.0% of population attributable risk. The presence of all four compared to zero CVD-RF was associated with a 9.6 years shorter expected survival for a man aged 50.

Conclusions
Most CVD deaths could be avoided by prevention of four traditional CVD-RF. Reduction of smoking prevalence and avoidance of weight gain in the population are the most effective measures. Particular attention should be dedicated to persons with multiple CVD-RF.

Keywords: Cardiovascular disease mortality; risk factors; MONICA; Switzerland; expected survival; population attributable risk

Introduction

Worldwide, cardiovascular disease (CVD) is the leading cause of death (1). One of the first studies elaborating the joint impact of risk factors (RF) on CVD was the Framingham study (2). These "traditional" RF include smoking, obesity, high blood pressure and high cholesterol (2). Framingham and most other studies have focused on non-fatal and fatal myocardial infarction (2-6). In contrast, the European SCORE project is based on CVD mortality, offering the advantage of a more reliable end-point (7). Another advantage is that SCORE relies on traditional RF which are easy to assess and to reproduce. Also, the assessment of these CVD-RF is part of routine medical check-ups aiming at an individual risk estimation.

The population burden associated with CVD-RF substantially vary between countries (3, 7, 8). In order to plan targeted prevention measures in a population, it is important to know the respective significance of CVD-RF and their combined impact on CVD mortality. For most countries, no specific information is available on the population level. The adoption of relative and population attributable risks (PAR) from other countries may be problematic because this could lead to inappropriate and ineffective public health measures. As there is no representative cohort in this country, there is only little evidence about how (much) traditional CVD-RF contribute to mortality in the Swiss population. It is also unknown whether the RF remain predictive for CVD-mortality after 25 years when they are only measured once at baseline. Commonly used CVD risk calculators are based on algorithms from Germany (9), a country with a different CVD-RF and mortality profile (8). In Switzerland, CVD mortality has dramatically decreased over the past three decades resulting in internationally very low rates (8). Counterintuitively, this apparently occurred without antecedent decrease in CVD-RF (10-12). We aimed at determining the impact of four traditional CVD-RF on CVD mortality in Switzerland and their population burden in terms of PAR and survival. Now for the first time, this is possible thanks to an anonymous record linkage with census and mortality data (see below), allowing a mortality follow-up of over 90% of participants of the Swiss MONICA (MONItoring of trends and determinants in CArdiovscular disease) study. The combined database includes socio-demographic, behavioural and clinical parameters offering the possibility to consider potential confounders and interactions.

Methods

Population

The studied population stems from MONICA, an international multicentre project initiated and coordinated by the World Health Organization (WHO) (13) . In Switzerland, the study has been conducted in three waves between 1983 and 1992 (14, 15). In this country, the "standard" MONICA age range of 25-64 years at baseline has been expanded to 25-74 years. Sampled persons were invited to attend a health examination in their community of residence and to complete a self-administered questionnaire. The participation rate varied between 54 and 78% (16). As in most MONICA centres, it was missed to provide for a mortality follow-up of the general population participating in the MONICA risk factors study. This shortcoming could be overcome by an anonymous record linkage with the Swiss National Cohort (16, 17). 9,853 (97.8%) of the eligible 10,160 MONICA participants could be linked with a census, mortality and/or emigration record, for details see (16). Details of the study population are given in **Table 1**.

CVD-RF

Measurements and blood sampling procedures were described (14, 15). In order to give an impression about the graduation of the association with CVD-mortality, we divided each of the four selected CVD-RF into four categories. We used the ratio of total cholesterol/HDL-cholesterol because among the available lipid parameters, this ratio was the strongest predictor of fatal ischemic heart disease (18). We used the following cut-offs for descriptive analyses: <5.0, 5.0-6.4, 6.5-7.9, ≥ 8.0 mmol/l. Blood pressure was categorized according to (19) (**Table 1**). For smoking status we used the categories never, former, light (<20 cig./d), heavy (≥ 20 cig./d). BMI was calculated from measured height (cm) and weight (kg) by dividing weight by height squared (kg/m^2) and into <25, 25-29.9, 30-34.9, ≥35 kg/m^2 according to the WHO (20). In order to obtain a sufficient number of CVD deaths in the CVD-RF combinations, we additionally collapsed the four categories into two groups (not underlined=not at risk vs. underlined=at risk in **Figure 1**) for analyses hereafter. This categorization corresponded to the cut-offs used for CVD risks in most other studies (smoking, blood pressure ≥ 140/90 mmHg, cholesterol ratio ≥ 5, obesity).

Covariates

Among the large number of available questions we selected two (healthy eating und sport) as proxy for a healthy lifestyle. Both of them significantly contributed to prediction of CVD-mortality in a model including "classical" RF. and had fewer missing values than other available lifestyle variables. Healthy eating pattern was defined when the answers to the question "Which meals do you eat during weekdays?" was "breakfast, lunch and dinner". Sport frequency was obtained with the question: "How often do you do sports?". Possible answers were: "every day, several times per week, once per week, less frequent, never". Blood pressure treatment was obtained

from: “During the past two weeks have you taken drugs in order to lower your blood pressure?” The following educational classes were used: i “Mandatory”: elementary schooling (corresponding to completed 8th US grade) or less (International Standard Classification of Education, ISCED 1 and 2); ii “Secondary”: vocational training or high school (completed 12th US grade; ISCED 3); iii “Tertiary”: technical college, upper vocational or university education (ISCED 5) (21). For marital status the categories “single”, “married”, “separated or divorced” and “widowed” were available.

End-point
CVD were defined according to ICD (International Classification of Diseases) revisions 8 (ICD-8: 390-458) and 10 (ICD-10: I00-I99). In Switzerland ICD-8 was used until 1994 followed by ICD-10 thereafter.

Statistical analyses
For descriptive analyses, we calculated counts, means and proportions of the variables of interest. We obtained hazard ratios (HR) of the four dichotomized CVD-RF variables using Cox proportional hazards models. The proportional hazards assumption was tested and appeared to be widely fulfilled. In order to make all models comparable, individuals with missing values in any of the covariates (n=9,375) were deleted for this part of the analysis. In all models we adjusted for age, sex and survey wave. In a second step, we additionally included other covariates; in a third step we additionally adjusted for the respective other CVD-RF variables.
We generated Cox models including a variable with the number of CVD-RF (0-4) and alternatively, including a variable with all possible combinations of smoking, high blood pressure and high cholesterol ratio. Unfortunately there were not enough persons being obese without having other CVD-RF to allow robust analyses. Therefore combinations with obesity are missing in **Figure 2**. The results of a Cox model (adjusted for age, sex and study wave, four vs. zero risk factors) with all-cause instead of CVD mortality was used to estimate mean residual survival. As this requires that all other covariates have to be fixed, we set them to wave 1, male sex and age fixed at 50 years at baseline. As the mean survival time is undefined for censored data, we have set the maximum observation period to 40 years. The obtained mean residual survival represents the expected number of years within this period.
Population attributable risk (PAR) for each of the four binary risk factors and for their combination was calculated as suggested in (22), using the results of a logistic regression model for CVD-mortality including sex, age, study wave and the four risk factors as covariates. General descriptive analyses and survival estimations were performed with Stata 11 (Stata Corp, Texas, USA, 2009), attributable deaths and mean residual lifetime were obtained with R 2.13.0 (The R Foundation for Statistical Computing, 2011).

Results

Descriptive analyses
Characteristics of participants and number of missing values are summarized in **Table 1**. There were substantially more CVD deaths and prevalence of risk factors was higher among men than among women. Among men, the proportion of heavy smokers was twice as high and the prevalence of high blood pressure and cholesterol ratio was also much higher. Large sex differences were also found for overweight but not for obesity. In contrast, differences regarding hypertension treatment, diet, physical activity, education and marital status were smaller. Compared to men, women had in average a lower educational class and a higher proportion was widowed. **Figure 1** shows the four CVD-RF categorized into four severity levels, with the respectively lowest category as reference. In none of the four CVD-RF, risk increase for the second lowest category reached statistical significance. The third category showed an increase in relative risk, but the association was only statistically significant for cholesterol ratio 6.5-7.9 and obesity class I. The relative risks of the highest categories were comparable. The highest relative risks were found for BMI $\geq$ 35 kg/m^2 and heavy smoking.

Multivariable adjusted analyses
Table 2 shows the HR of CVD-RF obtained from three models with increasing number of covariates. Further adjustment for lifestyle factors and socioeconomic status (SES; model two) moderately attenuated the relative risk of obesity and smoking, whereas that of high cholesterol ratio and blood pressure remained unchanged. Additional adjustment for medication changed the hazard ratio of high blood pressure only marginally: HR 1.29 (95% CI: 1.05-1.59). Additional adjustment for the respective other CVD-RF increased the relative risk of obesity and smoking but decreased that of high cholesterol ratio and blood pressure. In model three, obesity was only adjusted for smoking, because high blood pressure and cholesterol are on the leading pathway between obesity and death. Including these intermediate risk factors would result in over-adjustment and potential difficulties due to multicollinearity. In explorative analyses, obesity remained significantly associated with increased CVD death even after additional adjustment for high blood pressure and high cholesterol ratio (HR 1.57; 1.24-2.00). In addition, the respective PAR adjusted for age and sex is given. In contrast to the HR, PAR were higher for high blood pressure and high cholesterol ratio than for obesity and smoking.Based on a logistic

regression model including all CVD-RF, the joint PAR (22) was 43.0%. The corresponding PAR for 15 years of follow-up was 46.0% (Table A2).

Combination of CVD-RF
As shown in **Figure 2,** the combination of high blood pressure with high cholesterol ratio only moderately increased the risk compared to high blood pressure alone, suggesting common pathways. In contrast, the combination of either high blood pressure or cholesterol ratio with smoking substantially increased mortality risk. In fact, as shown in **Table A1** (Appendix), the correlation between high cholesterol ratio and high blood pressure was somewhat stronger than that between smoking and either high blood pressure or high cholesterol ratio. However, the correlation between the CVD-RF was generally weak. Relative risks associated with the number of present CVD-RF (irrespective of type) are shown in **Figure 3.** The risk increase associated with any of the CVD-RF was small but statistically significant and the presence of one additional CVD-RF only moderately increased the HR. The increase from two to three and from three to four CVD-RF was comparably stronger. Corresponding survival curves **(Appendix, Figure A1)** show the survival probabilities over study time for fixed other covariates. Estimations of life expectancy based on the same model for all-cause mortality showed that the expected further survival after age 50 in men with none of the four CVD-RF was 35.8 years compared to 26.2 years in men with simultaneously all four CVD-RF.

Discussion

Main results
This is the first study examining the impact of classical risk factors on CVD mortality in a general population in Switzerland. The CVD-RF obesity and smoking markedly increased the risk of cardiovascular death. This association remained significant after adjustment for lifestyle factors and SES and other CVD-RF. The impact on CVD death of the CVD-RF high blood pressure and particularly of high cholesterol ratio was weaker (**Table 2**). The combination of smoking with any other CVD-RF was particularly hazardous **(Figure 2)**. CVD-RF had a synergistic effect when combined: The risk increase between zero and two CVD-RF was weaker than that from two to four CVD-RF. The combination of all four CVD-RF resulted in an almost fivefold relative risk increase and – for a man aged 50– in a 9.6 years shorter survival. The PAR of 43% arising from all four CVD-RF (**Table 2**) suggests that a large proportion of CVD deaths in the population could be avoided. .

Comparison of CVD-RF
In line with our result, in Australia and Finland, smoking and (central) obesity were more strongly associated with CVD and coronary heart disease (CHD) mortality than blood pressure and high cholesterol ratio (23, 24). In the Whitehall study (UK), the HR of CVD death for the highest quintile of systolic blood pressure was larger than that for smoking and the highest quintile of cholesterol and BMI, the latter three having a similar magnitude (25). A similar pattern was found in the Seven Countries Study (US) (26). Using other measures of adiposity than BMI could (23) or could not (26, 27) increase predictiveness for CVD. In a study from Chicago (USA), CHD death was more strongly associated with a 20 mmHg increase in blood pressure than with smoking or a 1.03 mmol/L increase in blood cholesterol (28). Similarly, the ESC SCORE calculated an almost threefold CVD mortality risk increase from the lowest to the highest blood pressure category, whereas the increase was only twofold from the lowest to the highest cholesterol ratio category and for smoking vs. non-smoking (7).
In the INTERHEART and two European studies, smoking was the most significant CVD-RF of CHD events (4) (3, 5). In contrast, in the German MONICA cohort the HR for CHD events of hypertension and cholesterol ratio ≥5.5 were comparable and were higher than the HR of smoking (6). The Framingham cohort showed similar impact of hypertension, smoking and dyslipidemia on CHD events (2).

Adjustment of CVD-RF
The effect of obesity was only marginally affected by adjustment for lifestyle and SES and remained significantly associated with increased mortality after considering high blood pressure and cholesterol ratio (**Table 2**). However, only a part of CHD mortality risk associated with obesity is mediated by these intermediate CVD-RF (24, 28). Similar results were also found for non-fatal CVD events (29). In a meta-analysis of 21 cohort studies, half of the increased risk of CHD events in overweight and obese persons was explained by higher blood pressure and cholesterol levels (30). A substantial proportion of the effect of cholesterol ratio appears accounted for by other CVD-RF, suggesting that it could partially be a consequence of smoking and/or obesity. In contrast, after full adjustment, the decrease of HR of high blood pressure was small, indicating that this CVD-RF could be more independent of other RF. The HR of smoking remained virtually unaffected by adjustment. In fact, smokers were less frequently obese than non-smokers (31).

Combination of CVD-RF

A study with end-point CVD death found a twofold relative increase for the combination of high blood pressure and cholesterol and a threefold relative increase for the combination of high blood pressure and cholesterol with smoking (25). This was almost identical to our figures (**Figure 2**). Similar magnitudes of these CVD-RF (two or three of any of them) were found in another study with CVD death as end-point (32). Based on ESC SCORE, the 10-year risk of CVD death associated with blood pressure, cholesterol and smoking in persons aged 55-65 years is ten times higher in the highest than in the lowest risk group (7). The SCORE however compared larger extremes of blood pressure (<120 vs. ≥180 mmHg) and cholesterol ratio (<3 vs. ≥7) categories (7). Studies analysing fatal and non-fatal CHD resulted in substantially higher HR than ours (3, 5, 6). A study assessing CHD mortality risk also found higher relative increases for combinations of CVD-RF (28). When used in combination, "traditional" CVD-RF were highly predictive for CVD events (3-6, 23, 25, 27) and only few of them are necessary for prediction(23, 27). Additional inclusion of "novel" CVD-RF only minimally added to predictiveness (33, 34).
As found by others (6, 25, 28) the combination of smoking with either high blood pressure or high cholesterol ratio resulted in higher HR than the combination of high blood pressure with high cholesterol ratio. This suggests more common pathways in the latter two. Nevertheless the increase from zero to four CVD-RF suggests that each CVD-RF contributes to CVD-mortality and at least in part independently from the other ones (**Figure 3**). This is also supported by the relatively weak correlations of the considered CVD RF (**Table A1**). The fact that inclusion of obesity in addition to blood pressure and cholesterol ratio increased HR was at odds with a study showing that obesity failed to improve fatal and non-fatal CVD risk prediction when blood pressure and lipids and history of diabetes were available (27).

Attributable deaths and survival
Our study showed substantial potential for reduction of CVD deaths by prevention of four CVD-RF (**Table 2** and **Figure 3**). In the US, a part of the decrease in CVD death between 1980 and 2000 was attributable to reduction in cholesterol (24%), blood pressure (20%) and smoking prevalence (12%) (35). Studies with fatal and non-fatal CVD-end-points (6) and including a larger number of CVD-RF (3-5) reported attributable risks of 65%, 85% or more. These larger figures could also relate to the fact that we considered a longer follow-up time. In fact, limiting the follow-up time to 15 instead of 25 years in our study increased the PAR (Table A2, appendix). Moreover, in Switzerland, the prevalence of most CVD-RF can be expected to be lower than in other countries (8, 36). It is nevertheless surprising that even in "low prevalence" countries such as Switzerland, four classical CVD-RF contribute to almost 50% of excess CVD deaths.
As shown in the Whitehall study, men aged 50 years with the combination of smoking with high blood pressure and high cholesterol had in average a 10 years shorter survival than peers without these risk factors (25). This was comparable to our result. Similar figures were found in Chicago (9 years in men, 7 years in women) (32) and in five large US cohorts (6-10 years) (37). From a public health perspective this is an important finding because these risk factors are common in the population. At the same time, CVD-RF are easily detectable in clinical practice in a cost-efficient manner. Moreover CVD-RF are modifiable to a large extent and are thus widely avoidable.

Limitations
The MONICA participants included in our study had a lower mortality (in particular CVD mortality) than the general Swiss population (16). We also had only one assessment of exposure at study entry and could not consider changes occurring during follow-up. There was also lack of information on whether individuals with CVD-RF followed the advice that has been given upon study inclusion (e.g. cholesterol or blood pressure lowering treatment). The information about lifestyle factors relevant for CVD was limited. For example, we had only information on diet from a 24h recall and there was no information about the amount of alcohol consumed. Moreover, the number of missing answers varied between questions (**Table 1**). Our estimate of diet and physical activity was also rather coarse. However, both contributed to prediction of CVD mortally independently of "classical" RF. Our end-point was limited in the sense that we were restricted to fatal CVD. CVD mortality data from death certificates is reliable for young and middle aged persons but may cause misclassification in elderly, potentially leading to an underestimation of associated risk (38). Admittedly, the respective significance of risk factors could also depend on considered follow-up time (39). As suggested by our separate analyses, it is likely that the HR are larger in studies with repeated measurements or shorter follow-up time and that the association of a RF with the endpoint "washes out" over time. However, the differences between 25 years (**Table 2**) and 15 years of follow-up (**Table 2A**, Appendix) were relatively small and the overall pattern remained the same.
The statistical power was too weak to consequently allow separated analyses by age class or by sex. For certain strata the small number of CVD deaths precluded robust analyses, e.g. for obese smokers or non-smokers without any other CVD-RF. Comparisons of CVD mortality with CHD mortality must be interpreted with caution because these outcomes may not follow the same underlying pathways. Finally, limiting to only fatal end-ponts may not capture the significance of CVD-RF in its full spectrum.

Conclusions and public health implications

The majority of excess CVD deaths may be prevented by avoiding four risk factors. Smoking prevention is most effective, because measures are inexpensive and readily realizable, e.g. by public smoking ban or restricting access to cigarettes. Smoking is a particularly high risk when combined with high blood pressure and/or high cholesterol ratio. Therefore smokers should be intensively screened and treated at lower thresholds. Large prevention potential would arise from reducing weight in obese persons, but this is not realistic. Because overweight was not associated with an increased risk, efforts aimed at avoiding weight gain and improving health behaviour appear more promising. Avoiding obesity is important because by controlling and treating high blood pressure and cholesterol, excess mortality risk can only be decreased but not eliminated. Aggressive treatment in persons having only one RF can be disputed. However, because of their synergistic impact on mortality, accumulation of three or more risk factors should be avoided. Because it is non-invasive and easily conductible, population screening of high blood pressure should be intensified, also in persons without apparent RF like obesity or smoking.

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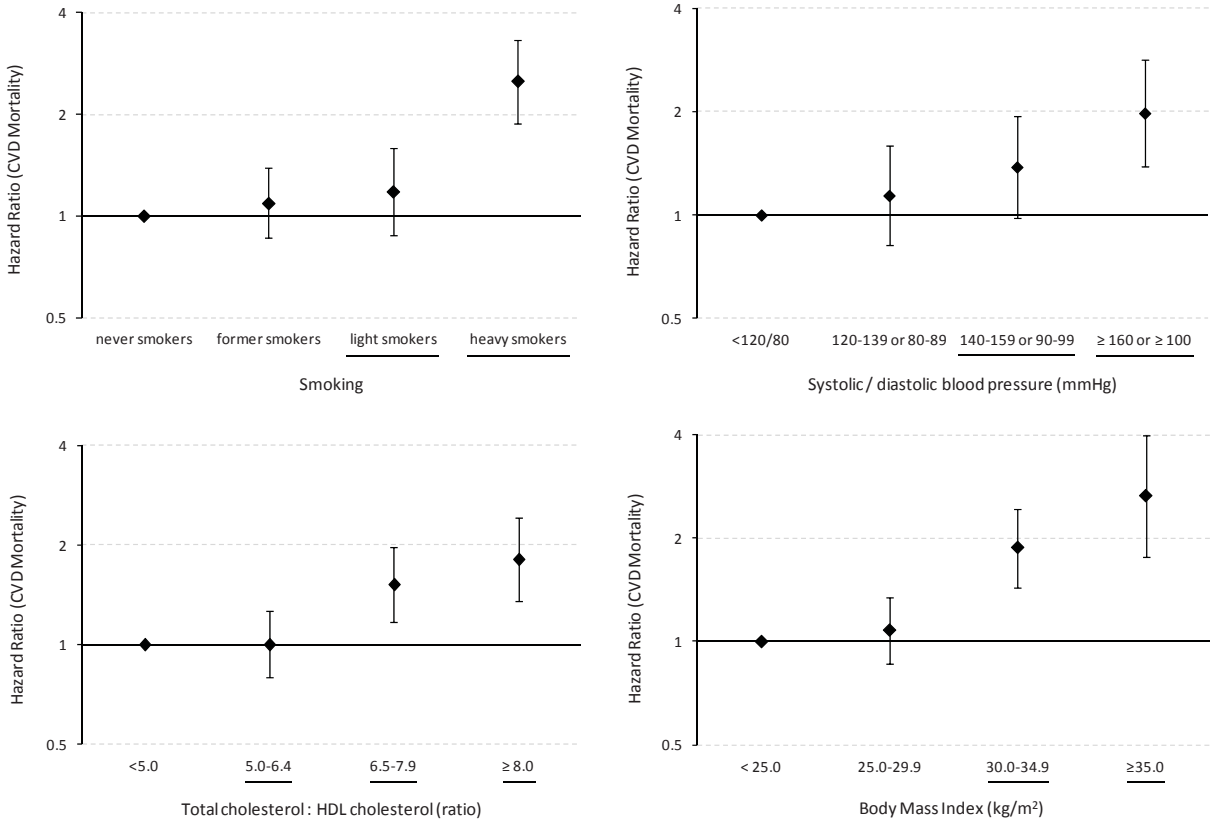
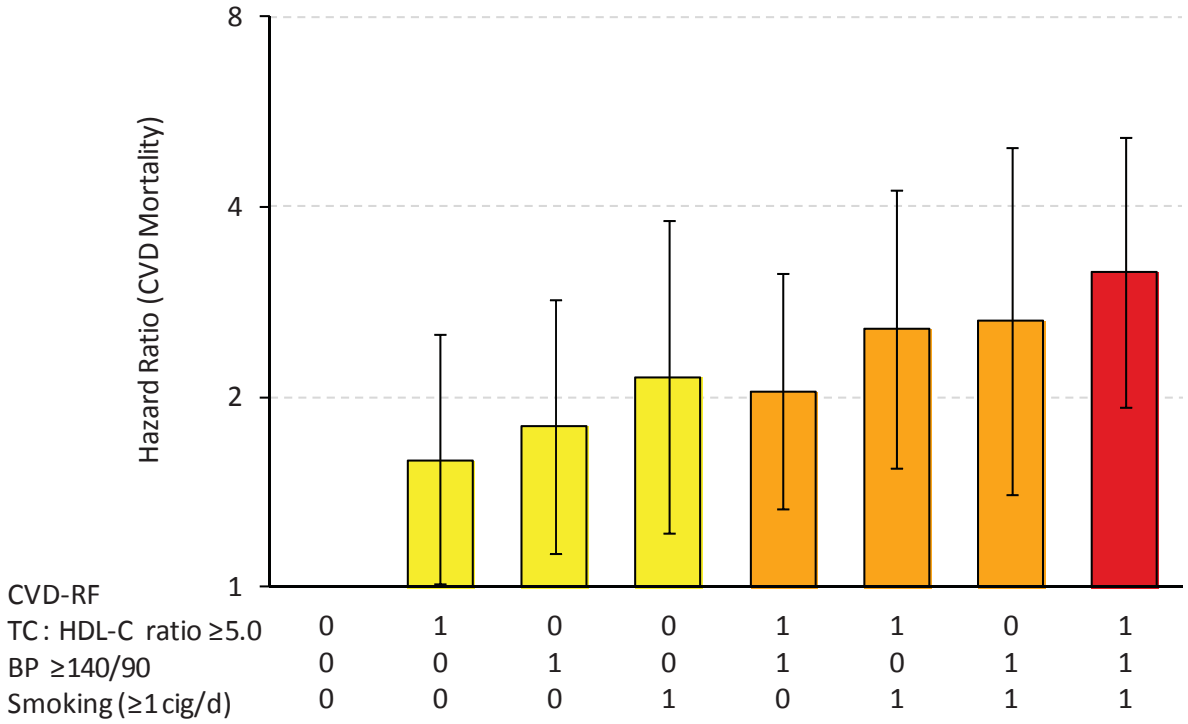
Figure legends

Figure 1. Age and sex adjusted relative risk of CVD death by severity of CVD-RF, 9,375 participants of the Swiss MONICA study, 1983-92, 25-74 years at baseline



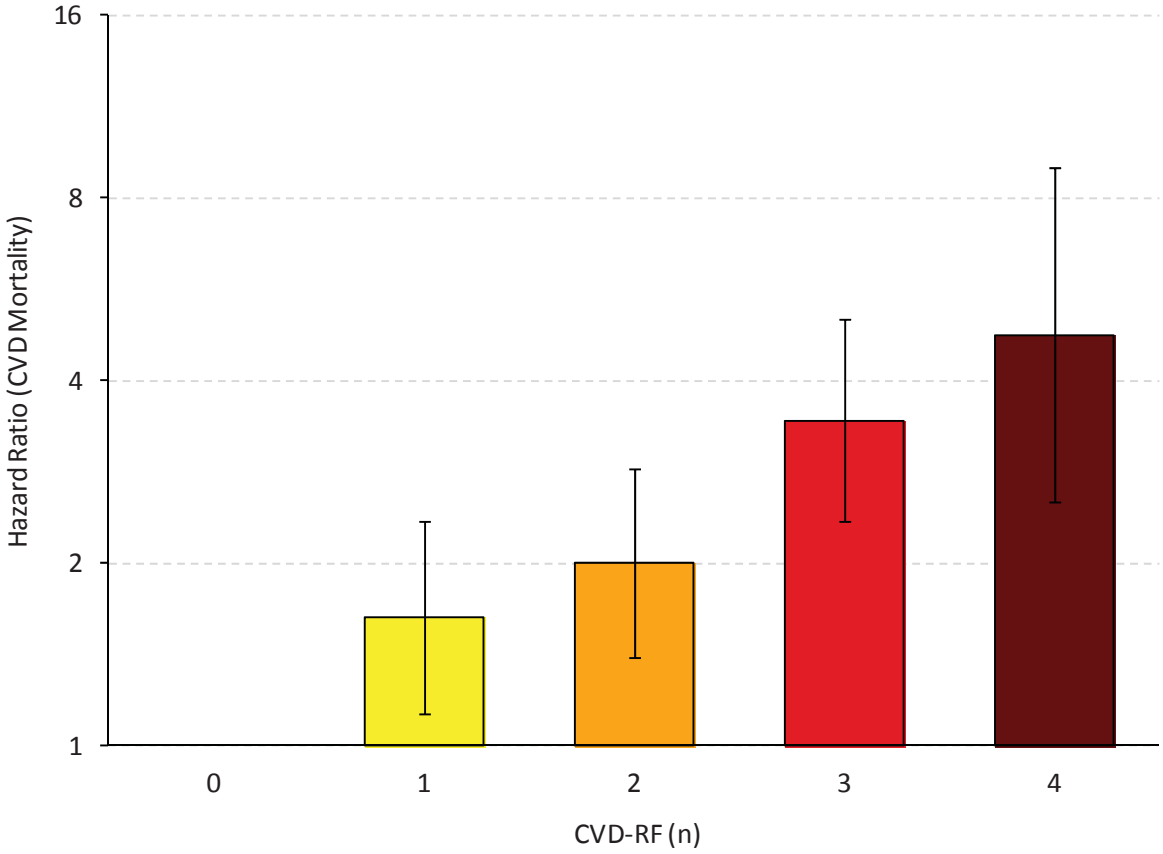
Reference is the respective lowest category, for the following tables and figures, risk categories were dichotomized (underlined: at risk vs. not underlined: not at risk)
CVD-RF: Cardiovascular disease risk factors; MONICA: MONItoring of trends and determinants in CArdiovscular disease

Figure 2. Age and sex adjusted relative risk for CVD death by risk factor combination, 9,375 participants of the Swiss MONICA study, 1983-92, 25-74 years at baseline



Reference category is the first combination (0, 0, 0). BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol.

Figure 3 Age and sex adjusted relative risk of CVD death by number of CVD-RF, 9,375 participants of the Swiss MONICA study, 1983-92, 25-74 years at baseline



Reference category is 0. CVD-RF include smoking (≥ 1 cig/d); high blood pressure (≥140 or ≥90); high total cholesterol: high-density lipoprotein cholesterol ratio (≥ 5.0); obesity (body mass index ≥30 kg/m^2).

Table 1. Characteristics (counts, means and proportions) of the study population, Swiss MONICA study, 1983-92, 25-74 years at baseline

	Men	Women	All	Missings (n)
Participants (n)	4969	4884	9853	
Mean age (years)	47.0	47.3	47.2	
Deaths (n)				
CVD	280	168	448	
All causes	945	581	1526	
CVD-RF				
Smoking				31
Never smokers (%)	29.3	51.2	40.1	
Former smokers (%)	33.5	19.7	26.7	
Current light smokers (<20 cig./d, %)	15.0	18.5	16.7	
Current heavy smokers (≥20 cig./d, %)	22.3	10.6	16.5	
Blood pressure (systolic / diastolic, mmHg)				21
<120/80 (%)	19.5	37.0	28.2	
120–139 or 80–89 (%)	46.0	40.0	43.0	
140–159 or 90-99 (%)	25.0	16.3	20.6	
≥160 or ≥100 (%)	9.6	6.7	8.2	
Total Cholesterol : HDL-Cholesterol				355
Mean (ratio)	5.7	4.4	5.1	
<5.0 (%)	41.5	73.2	57.3	
5.0-6.4 (%)	31.7	17.9	24.8	
6.5-7.9 (%)	16.4	6.0	11.2	
≥8.0 (%)	10.4	2.9	6.7	
Body Mass Index (BMI)				16
Mean (kg/m^2)	26.3	24.8	25.5	
<25 (%)	38.0	59.0	48.4	
25-29.9 (%)	47.7	28.7	38.3	
30-34.9 (%)	12.4	8.9	10.6	
≥35 (%)	1.9	3.4	2.7	
Covariates				
Three main meals daily (%)	64.2	74.4	69.2	3
Sport				33
Every day (%)	3.2	3.9	3.5	
Several times per week (%)	18.6	13.3	16.0	
Once per week (%)	21.4	23.2	22.3	
Less frequent (%)	25.2	19.8	22.5	
Never (%)	31.5	39.9	35.7	
Educational class				29
Tertiary (%)	23.2	15.3	19.3	
Upper secondary (%)	52.6	44.8	48.7	
Mandatory and secodary (%)	24.2	39.9	32.0	
Marital Status				9
Single	9.1	9.0	9.0	
Married	84.3	76.4	80.4	
Widowed	1.4	7.0	6.5	
Separated or divorced	5.3	7.6	4.2	
Hypertension treatment (%)	11.2	12.7	11.9	117

CVD-RF, Cardiovascular disease risk factors; MONICA, MONItoring of trends and determinants in CArdiovscular disease

Table 2. Relative risk of CVD death of selected risk factors increasingly adjusted with three models, 9,375 participants of the Swiss MONICA study, 1983-92, 25-74 years at baseline

Model (adjustment)	1 (age, sex)			2 (1 + lifestyle, SES)*		3 (2 + other CVD-RF)**	
	PAR (%)	HR	95% CI	HR	95% CI	HR	95% CI
CVD-RF:							
Obesity (BMI ≥30 kg/m^2)	11.9	1.86	1.50-2.31	1.75	1.41-2.18	1.81	1.46-2.25
Smoking (current, light and heavy)	11.1	1.63	1.32-2.01	1.52	1.23-1.89	1.58	1.27-1.96
High blood pressure (≥ 140 or ≥ 90)	14.5	1.42	1.16-1.73	1.41	1.16-1.73	1.34	1.10-1.64
High TC:HDL-C ratio (≥ 5.0)	15.3	1.30	1.06-1.60	1.31	1.07-1.61	1.17	0.95-1.44

Model 1 (basic): adjusted for age and sex. Model 2 (lifestyle and socioeconomic status): model 1 additionally adjusted for three meals per day, physical activity, education, and marital status. The HR of high blood pressure changed to 1.29 (95% CI 1.05–1.59) after adjustment for blood pressure-lowering medication. Model 3 (cardiovascular disease risk factors): model 2 additionally adjusted for the other risk factors (obesity: number of cigarettes; smoking: BMI, TC/HDL-C ratio, systolic blood pressure; high TC/HDL-C ratio: BMI, systolic blood pressure, number of cigarettes; high blood pressure: BMI, TC/HDL-C ratio, number of cigarettes). Obesity was only adjusted for smoking, additional adjustment for blood pressure and cholesterol ratio resulted in a HR of 1.57 (95% CI 1.24–2.00). BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; PAR, population attributable risk.

Appendix

Table A1. Correlation coefficients of the binary and continuous variables, 9,375 participants of the Swiss MONICA study, 1983-92, 25-74 years at baseline

Variable (binary)	Obesity	Smoking	High blood pressure	High TC/HDL-C ratio
Obesity (BMI ≥30 kg/m2)	1			
Smoking (current, light and heavy)	0.07	1		
High blood pressure (≥ 140 or ≥ 90)	0.17	0.05	1	
High TC:HDL-C ratio (≥ 5.0)	0.18	0.07	0.17	1

All p-values are <0.001, calculated with the "Phi" command (correlation of binary variables) of STATA

Variable (cotinuous)	BMI	Smoking	Systolic blood pressure	TC/HDL-C ratio
BMI (in kg/m^2)	1			
Smoking (number of cigarettes)	-0.06	1		
Systolic blood pressure (in mmHg)	0.32	-0.02	1	
TC:HDL-C ratio	0.37	0.13	0.21	1

All p-values are <0.001, calculated with the "Pearson" command of STATA

Table A2. Relative risk of CVD death of selected risk factors increasingly adjusted with three models, 9,375 participants of the Swiss MONICA study, 1983-92, 25-74 years at baseline, follow-up time limited to 15 years

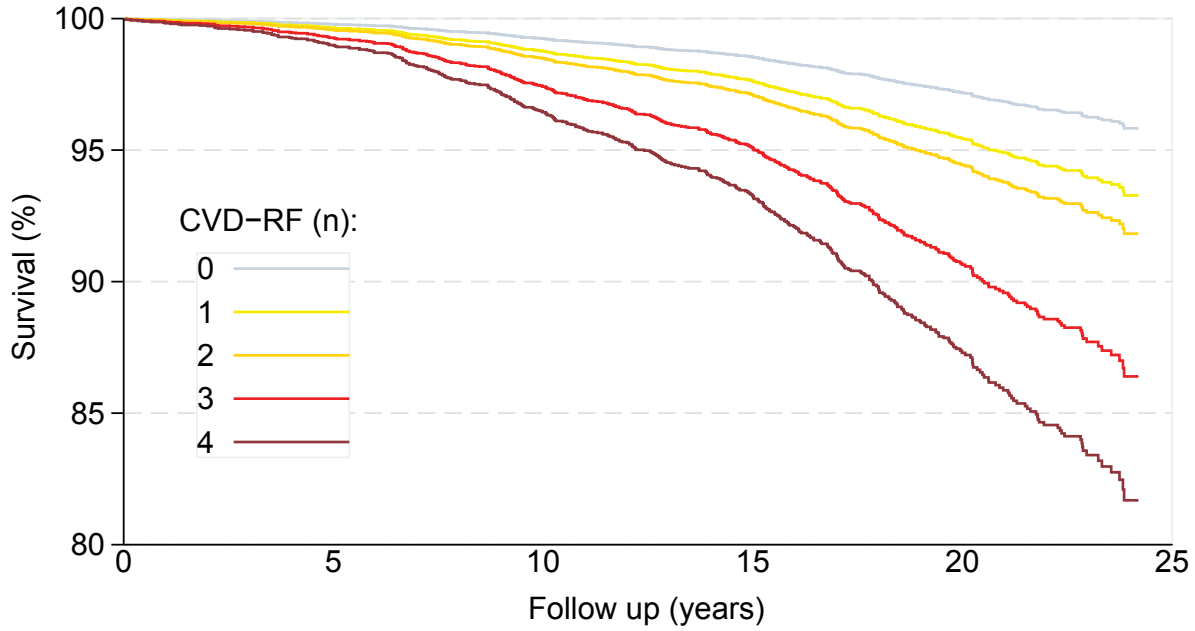
Model (adjustment):	1 (age, sex)			2 (1 + lifestyle, SES)*		3 (2 + other risk factors)**	
	PAR (%)	HR	95% CI	HR	95% CI	HR	95% CI
CVD-RF							
Obesity (BMI ≥30 kg/m^2)	15.0	1.95	1.49-2.56	1.8	1.36-2.37	1.87	1.42-2.46
Smoking (current, light and heavy)	14.2	1.74	1.33-2.29	1.61	1.22-2.12	1.71	1.29-2.26
High blood pressure (≥ 140 or ≥ 90)	13.9	1.43	1.10-1.85	1.42	1.10-1.84	1.32	1.02-1.72
High TC:HDL-C ratio (≥ 5.0)	14.1	1.33	1.02-1.74	1.34	1.02-1.75	1.16	0.88-1.53

*Lifestyle, socio-economic status (SES): additional adjustment for three meals per day, physical activity, education, marital status. The HR of high blood pressure changed to HR 1.29 (1.05-1.59) after adjustment of blood pressure lowering medication.

**Other risk factors: except of obesity, all risk factors were additionally adjusted for the respectively other risk factors (Obesity: number of cigarettes; Smoking: BMI, TC/HDL-C ratio, systolic blood pressure; High TC/HDL-C ratio: BMI, systolic blood pressure, number of cigarettes; high blood pressure: BMI, TC/HDL-C ratio, number of cigarettes). Obesity was only adjusted for smoking, additional adjustment of blood pressure and cholesterol ratio resulted in a HR of 1.57 (1.24-2.00).

CVD-RF, Cardiovascular disease risk factors; PAR, Population Attributable Risk (in %); TC, total cholesterol; HDL-C, high density lipoprotein cholesterol

Figure A1. Survival curves by number of CVD-RF, for wave 1, male sex and age fixed at 50, participants of the Swiss MONICA study, 1983-92, 25-74 years at baseline



MONICA: MONItoring of trends and determinants in CArdiovscular disease
Cardiovascular disease risk factors (CVD-RF) include smoking (current, light and heavy, ≥ 1 cig./d); high blood pressure (≥ 140 or ≥ 90); high TC/HDL-C ratio (≥ 5.0); obesity (BMI ≥30 kg/m^2)
TC: total cholesterol; HDL-C: high density lipoprotein cholesterol